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Remington: Practice of

ALFONSO R GENNARO
Chairman of the Editorial Board and Editor

The Science and Pharmacy

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Remington: The Science and Practice of Pharmacy . . . *a treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities of the pharmacist as the drug-information specialist of the health team . . . A textbook and reference work for pharmacists, physicians and other practitioners of the pharmaceutical and medical sciences.*

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Table 1—Rates of Entry of Drugs in CSF and the Degrees of Ionization of Drugs at pH 7.4[7]

Drug/chemical	% binding to plasma protein	pK_a[a]	% un-ionized at pH 7.4	Permeability constant ($P\ min^{-1}$) ± S.E.
Drugs mainly ionized at pH 7.4				
5-Sulfosalicylic acid	22	(strong)	0	<0.0001
N-Methylnicotinamide	<10	(strong)	0	0.0005 ± 0.00006
5-Nitrosalicylic acid	42	2.3	0.001	0.001 ± 0.0001
Salicylic acid	40	3.0	0.004	0.006 ± 0.0004
Mecamylamine	20	11.2	0.016	0.021 ± 0.0016
Quinine	76	8.4	9.09	0.078 ± 0.0061
Drugs mainly un-ionized at pH 7.4				
Barbital	<2	7.5	55.7	0.026 ± 0.0022
Thiopental	75	7.6	61.3	0.50 ± 0.051
Pentobarbital	40	8.1	83.4	0.17 ± 0.014
Aminopyrine	20	5.0	99.6	0.25 ± 0.020
Aniline	15	4.6	99.8	0.40 ± 0.042
Sulfaguanidine	6	>10.0[b]	>99.8	0.003 ± 0.0002
Antipyrine	8	1.4	>99.9	0.12 ± 0.013
N-Acetyl-4-aminoantipyrine	<3	0.5	>99.9	0.012 ± 0.0010

[a] The dissociation constant of both acids and bases is expressed as the pK_a; the negative logarithm of the acidic dissociation constant.

[b] Sulfaguanidine has a very weakly acidic group ($pK_a > 10$) and two very weakly basic groups (pK_a 2.75 and 0.5). Consequently, the compound is almost completely undissociated at pH 7.4.

for all practical purposes, only the un-ionized form is said to pass through the membrane. This has become known as the *principle of nonionic diffusion*.

This principle is the reason that only the concentrations of the un-ionized form of the barbiturates are plotted in Fig 9.

For the purpose of further illustrating the principle, Table 1 is provided.[7] In the table, the permeability constants for penetration into the cerebral spinal fluid of rats are higher for un-ionized drugs than for ionized ones. The apparent exceptions—barbital, sulfaguanidine and acetylaminoantipyrine—may be explained by the dipolarity of the un-ionized molecules. With barbital, the two lipophilic ethyl groups are too small to compensate for the considerable dipolarity of the un-ionized barbituric acid ring; also it may be seen that barbital is appreciably ionized, which contributes to the relatively small permeability constant. Sulfaguanidine and acetylaminoantipyrine are both very polar molecules. Mecamylamine also might be considered an exception, since it shows a modest permeability even though strongly ionized; there is no dipolarity in mecamylamine except in the amino group.

Absorption of Drugs

Absorption is the process of movement of a drug from the site of application into the extracellular compartment of the body. Inasmuch as there is a great similarity among the various membranes that a drug may pass through in order to gain access to the extracellular fluid, it might be expected that the particular site of application (or *route*) would make little difference to the successful absorption of the drug. In actual fact, it makes a great deal of difference; many factors, other than the structure and composition of the membrane, determine the ease with which a drug is absorbed. These factors are discussed in the following sections, along with an account of the ways that drug formulations may be manipulated to alter the ability of a drug to be absorbed readily.

Routes of Administration

Drugs may be administered by many different routes. The various routes include oral, rectal, sublingual or buccal, parenteral, inhalation and topical. The choice of a route depends upon both convenience and necessity.

Oral Route—This is obviously the most convenient route for access to the systemic circulation, providing that various factors do not militate against this route. Oral administration does not always give rise to sufficiently high plasma concentrations to be effective; some drugs are absorbed unpredictably or erratically; patients occasionally have an absorption malfunction. Drugs may not be given by mouth to patients with gastrointestinal intolerance, or who are in preparation for anesthesia or who have had gastrointestinal surgery. Oral administration also is precluded in coma.

Rectal Route—Drugs that ordinarily are administered by the oral route usually can be administered by injection or by the alternative *lower enteral* route, through the anal portal into the rectum or lower intestine. With regard to the latter, *rectal suppositories* or *retention enemas* formerly were used quite frequently, but their popularity has abated somewhat, owing to improvements in parenteral preparations. Nevertheless, they continue to be valid and, sometimes, very important ways of administering a drug, especially in pediatrics and geriatrics. In Fig 10[8] the availability of a drug by retention enema may be compared with that by the intravenous and oral route and rectal suppository administration. It is apparent that the retention enema may be a very satisfactory means of administration but that rectal suppositories may be inadequate where rapid absorption and high plasma levels are required. The illustration is not intended to lead the reader to the conclusion that a retention enema always will give more prompt and higher blood levels than the oral route; for converse findings for the same drug have been reported, but, rather, to show that the retention enema may offer a useful substitute for the oral route.

Sublingual or Buccal Route—Even though an adequate plasma concentration eventually may be achievable by the oral route, it may rise much too slowly for use in some situations where a rapid response is desired. In such situations parenteral therapy usually is indicated. However, the patients with angina pectoris may get quite prompt relief from an acute attack by the *sublingual* or *buccal* administration of nitroglycerin, so that parenteral administration may be avoided. When only small amounts of drugs are required to gain access to the blood, the buccal route may be very satisfactory, providing the physicochemical prerequisites for absorption by this route are present in the drug and dosage form. Only a few drugs may be given successfully by this route.

Parenteral Routes—These routes, by definition, include any route other than the oral–gastrointestinal (enteral) tract

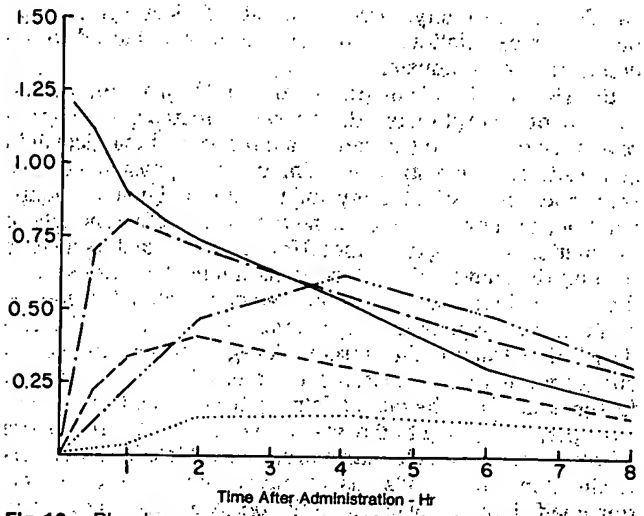

Fig 10. Blood concentration in mg/100 mL of theophylline (ordinate) following administration to humans of aminophylline in the amounts and by the routes indicated. Doses: per 70 kg. Theophylline-ethylenediamine by various routes: —— *intravenous, 0.5 g;* – – – *retention enema, 0.5 g;* — ··· — ··· — *oral tablets-Pl., 0.5 g;* -·- *oral tablets-Pl., 0.3 g;* ···· *rectal suppository, 0.5 g* (courtesy, Truitt *et al*,[8] adapted).

but in common medical usage the term excludes topical administration and includes only various hypodermic routes. Parenteral administration includes the intravenous, intramuscular and subcutaneous routes. Parenteral routes may be employed whenever enteral routes are contraindicated (see above) or inadequate.

The *intravenous* route may be preferred on occasion, even when a drug may be well-absorbed by the oral route. There is no delay imposed by absorption before the administered drug reaches the circulation, and blood levels rise virtually as rapidly as the time necessary to empty the syringe or infusion bottle. Consequently, the intravenous route is the preferred route when an emergency calls for an immediate response.

In addition to the rapid rise in plasma concentration of drug, another advantage of intravenous administration is the greater predictability of the peak plasma concentration, which, with some drugs, can be calculated with a fair degree of precision. Smaller doses generally are required by the intravenous than by other routes, but this usually affords no advantage, inasmuch as the sterile injectable dosage form costs more than enteric preparations and the requirements for medical or paramedical supervision of administration also may add to the cost and inconvenience.

Because of the rapidity with which drug enters the circulation, dangerous side effects to the drug may occur which are often not extant by other routes. The principal untoward effect is a depression of cardiovascular function, which is often called *drug shock*. Consequently, some drugs must be given quite slowly to avoid vasculotoxic concentrations of drug in the plasma. Acute, serious, allergic responses also are more likely to occur by the intravenous route than by other routes.

Many drugs are too irritant to be given by the oral, intramuscular or subcutaneous route and must, of necessity, be given intravenously. However, such drugs also may cause damage to the veins (phlebitis) or, if extravasated, cause necrosis (slough) around the injection site. Consequently, such irritant drugs may be diluted in isotonic solutions of saline, dextrose or other media and given by slow infusion, providing that the slower rate of delivery does not negate the purpose of the administration in emergency situations.

Absorption by the *intramuscular* route is relatively fast and this parenteral route may be used where an immediate effect is not required but a prompt effect is desirable. Intramuscular deposition also may be made of certain repository preparations, rapid absorption not being desired. Absorption from an intramuscular depot is more predictable and uniform than from a subcutaneous site.

Irritation around the injection site is a frequent accompaniment of intramuscular injection, depending upon the drug and other ingredients. Because of the dangers of accidental intravenous injection, medical supervision generally is required. Sterilization is necessary.

In *subcutaneous* administration the drug is injected into the alveolar connective tissue just below the skin. Absorption is slower than by the intramuscular route but, nevertheless, may be prompt with many drugs. Often, however, absorption by this route may be no faster than by the oral route. Therefore, when a fairly prompt response is desired with some drugs, the subcutaneous route may not offer much advantage over the oral route, unless for some reason the drug cannot be given orally.

The slower rate of absorption by the subcutaneous route is usually the reason why the route is chosen, and the drugs given by this route are usually those in which it is desired to spread the action out over a number of hours, in order to avoid either too intense a response, too short a response or frequent injections. Examples of drugs given by this route are insulin and sodium heparin, neither of which is absorbed orally and both of which should be absorbed slowly over many hours. In the treatment of asthma, epinephrine usually is given subcutaneously to avoid the dangers of rapid absorption and consequent dangerous cardiovascular effects. Many repository preparations, including tablets or pellets, are given subcutaneously. As with other parenteral routes, irritation may occur. Sterile preparations also are required. However, medical supervision is not required always and self-administration by this route is customary with certain drugs, such as insulin.

Intradermal injection, in which the drug is injected into, rather than below the dermis, is rarely employed, except in certain diagnostic and test procedures, such as screening for allergic or local irritant responses.

Occasionally, even by the intravenous route, it is not possible, practical or safe to achieve plasma concentrations high enough so that an adequate amount of drug penetrates into special compartments, such as the cerebrospinal fluid, or various cavities, such as the pleural cavity. The brain is especially difficult to penetrate with water-soluble drugs. The name *blood-brain barrier* is applied to the impediment to penetration. When drugs do penetrate, the choroid plexus often secretes them back into the blood very rapidly, so that adequate levels of drugs in the cerebrospinal fluid may be difficult to achieve. Consequently, *intrathecal* or *intraventricular* administration may be indicated.

Body cavities such as the pleural cavity normally are wetted by a small amount of effusate which is in diffusion equilibrium with the blood and, hence, is accessible to drugs. However, infections and inflammations may cause the cavity to fill with serofibrinous exudate which is too large to be in rapid diffusion equilibrium with the blood. *Intracavitary* administration, thus, may be required. It is extremely important that sterile and nonirritating preparations be used for intrathecal or intracavitary administration.

Inhalation Route—Inhalation may be employed for delivering gaseous or volatile substances into the systemic circulation, as with most general anesthetics. Absorption is virtually as rapid as the drug can be delivered into the alveoli of the lungs, since the alveolar and vascular epithelial membranes are quite permeable, blood flow is abundant and there is a very large surface for absorption.

Aerosols of nonvolatile substances also may be administered by inhalation, but the route is used infrequently for delivery into the systemic circulation because of various factors which contribute to erratic or difficult-to-achieve blood levels. Whether or not an aerosol reaches and is retained in pulmonary alveoli depends critically upon particle size. Particles greater than 1 μm in diameter tend to settle in the

bronchioles and bronchi, whereas particles less than 0.5 μm fail to settle and mainly are exhaled. Aerosols are employed mostly when the purpose of administration is an action of the drug upon the respiratory tract itself. An example of a drug commonly given as an aerosol is isoproterenol, which is employed to relax the bronchioles during an asthma attack.

Topical Route—Topical administration is employed to deliver a drug at, or immediately beneath, the point of application. Although occasionally enough drug is absorbed into the systemic circulation to cause systemic effects, absorption is too erratic for the topical route to be used routinely for systemic therapy. However, various transdermal preparations of nitroglycerin and clonidine are employed quite successfully for systemic use. Some investigations with aprotic solvent vehicles such as dimethyl sulfoxide (DMSO) also has generated interest in topical administration for systemic effects. A large number of topical medicaments are applied to the skin, although topical drugs are also applied to the eye, nose and throat, ear, vagina, etc.

In man, percutaneous absorption probably occurs mainly from the surface. Absorption through the hair follicles occurs, but the follicles in man occupy too small a portion of the total integument to be of primary importance. Absorption through sweat and sebaceous glands generally appears to be minor. When the medicament is rubbed on vigorously, the amount of the preparation that is forced into the hair follicles and glands is increased. Rubbing also forces some material through the stratum corneum without molecular dispersion and diffusion through the barrier. Rather large particles of substances such as sulfur have been demonstrated to pass intact through the stratum corneum. When the skin is diseased or abraded, the cutaneous barrier may be disrupted or defective, so that percutaneous absorption may be increased. Since much of a drug that is absorbed through the epidermis diffuses into the circulation without reaching a high concentration in some portions of the dermis, systemic administration may be preferred in lieu of, or in addition to, topical administration.

Factors That Affect Absorption

In addition to the physicochemical properties of drug molecules and biological membranes, various factors affect the rate of absorption and determine, in part, the choice of route of administration.

Concentration—It is self-evident that the concentration, or, more exactly, the thermodynamic activity, of a drug in a drug preparation will have an important bearing upon the rate of absorption, since the rate of diffusion of a drug away from the site of administration is directly proportional to the concentration. Thus, a 2% solution of lidocaine will induce local anesthesia more rapidly than a 0.2% solution. However, drugs administered in solid form are not absorbed necessarily at the maximal rate (see *Physical State of Formulation and Dissolution Rate*, below).

After oral administration the concentration of drugs in the gut is a function of the dose, but the relationship is not necessarily linear. Drugs with a low aqueous solubility (eg, digitoxin) quickly saturate the gastrointestinal fluids, so that the rate of absorption tends to reach a limit as the dose is increased. The peptizing and solubilizing effects of bile and other constituents of the gastrointestinal contents assist in increasing the rate of absorption but are in themselves somewhat erratic. Furthermore, many drugs affect the rates of gastric, biliary and small intestinal secretion, which causes further deviations from a linear relationship between concentration and dose.

Drugs that are administered subcutaneously or intramuscularly also may not always show a direct linear relationship between the rate of absorption and the concentration of drug in the applied solution, because osmotic effects may cause dilution or concentration of the drug, if the movement of water or electrolytes is different from that of the drug. Whenever possible, drugs for hypodermic injection are prepared as isotonic solutions. Some drugs affect the local blood flow and capillary permeability, so that at the site of injection there may be a complex relationship of concentration achieved to the concentration administered.

Physical State of Formulation and Dissolution Rate—The rate of absorption of a drug may be affected greatly by the rate at which the drug is made available to the biological fluid at the site of administration. The intrinsic physicochemical properties, such as solubility and the thermodynamics of dissolution, are only some of the factors which affect the rate of dissolution of a drug from a solid form. Other factors include not only the unavoidable interactions among the various ingredients in a given formulation but also deliberate interventions to facilitate dispersion (eg, comminution, Chapter 83 and dissolution, Chapter 34) or retard it (eg, coatings, Chapter 93 and slow-release formulations, Chapter 94). There also are factors that affect the rate of delivery from liquid forms. For example, a drug in a highly viscous vehicle is absorbed more slowly from the vehicle than a drug in a vehicle of low viscosity; in oil-in-water emulsions, the rate depends upon the partition coefficient. These manipulations are the subject of biopharmaceutics (see Chapter 94).

Area of Absorbing Surface—The area of absorbing surface is an important determinant of the rate of absorption. To the extent that the therapist must work with the absorbing surfaces available in the body, the absorbing surface is not subject to manipulation. However, the extent to which the existing surfaces may be used is subject to variation. In those rare instances in which percutaneous absorption is intended for systemic administration, the entire skin surface is available.

Subsequent to subcutaneous or intramuscular injections, the site of application may be massaged in order to spread the injected fluid from a compact mass to a well-dispersed deposit. Alternatively, the dose may be divided into multiple small injections, although this recourse is generally undesirable.

The different areas for absorption afforded by the various routes account, in part, for differences in the rates of absorption by those routes. The large alveolar surface of the lungs allows for extremely rapid absorption of gases, vapors and properly aerosolized solutions; with some drugs the rate of absorption may be nearly as fast as intravenous injection. In the gut the small intestine is the site of the fastest, and hence most, absorption because of the small lumen and highly developed villi and microvilli; the stomach has a relatively small surface area, so that even most weak acids are absorbed predominately in the small intestine despite a pH partition factor that should favor absorption from the stomach (see *The pH Partition Principle*, page 715).

Vascularity and Blood Flow—Although the thermal velocity of a freely diffusible average drug molecule is on the order of meters per second, in solution the rate at which it will diffuse away from a reference point will be much slower. Collisions with water and/or other molecules, which cause a random motion, and the forces of attraction between the drug and water or other molecules slow the net mean velocity.

The time taken to traverse a given distance is a function of the square of the distance; on the average it would take about 0.01 second for a net outward movement of 1 μm, 1 second for 10 μm, 100 second for 100 μm, etc. In a highly vascular tissue, such as skeletal muscle, in which there may be more than 1000 capillaries/mm^2 of cross section, a drug molecule would not have to travel more than a few microns, hence, less than a second on the average, to reach a capillary from a point of extravascular injection.

Once the drug reaches the blood, diffusion is not important to transport and the rate of blood flow determines the movement. The velocity of blood flow in a capillary is about 1 mm/sec, which is 100 times faster than the mean net velocity of drug molecules 1 mm away from their injection site. The velocity of blood flow is even faster in the larger vessels. Overall, less than a minute is required to distribute drug molecules from the capillaries at the injection site to the rest of the body.

CHAPTER 86

Solutions, Emulsions, Suspensions and Extracts

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The dosage forms described in this chapter may be prepared by dissolving the active ingredient(s) in an aqueous or nonaqueous solvent, by suspending the drug (if it is insoluble in pharmaceutically or therapeutically acceptable solvents) in an appropriate medium or by incorporating the medicinal agent into one of the two phases of an oil and water system. Such solutions, suspensions and emulsions are further defined in subsequent paragraphs but some, with similar properties, are considered elsewhere. These dosage forms are useful for a number of reasons. They can be formulated for different routes of administration: oral use, introduction into body cavities or applied externally. The dose easily can be adjusted by dilution, and the oral liquid form readily can be administered to children or people unable to swallow tablets or capsules. Extracts eliminate the need to isolate the drug in pure form, allow several ingredients to be administered from a single source (eg, pancreatic extract) and permit the preliminary study of drugs from natural sources. Occasionally, solutions of drugs such as potassium chloride are used to minimize adverse effects in the gastrointestinal tract.

The preparation of these dosage forms involves several considerations on the part of the pharmacist: purpose of the drug; internal or external use; concentration of the drug, selection of the liquid vehicle, physical and chemical stability of the drug, preservation of the preparation and use of appropriate excipients such as buffers, solubilizers, suspending agents, emulsifying agents, viscosity controlling agents, colors and flavors. Oral preparations require that consideration be given to improving patient compliance by making an acceptable product; consequently, color, odor and taste must be considered. These organoleptic factors are described in Chapter 80. The viscosity of a product also must be considered in order that it has the proper palatability for an oral preparation and to have the appropriate suspending properties if it is an emulsion or suspension. The theory pertaining to these systems is provided in Chapters 21 and 22. The theory of solutions, which involves solubility, ionization, pH control through the use of buffers and solubilization, is discussed in Chapters 16 and 17. Because of the complexity of some manufactured products, compounding may be carried out with the aid of linear programming models in order to obtain the optimal product. Chapters (87 to 89) should be consulted for information on the preparation and characteristics of those liquid preparations that are intended for ophthalmic or parenteral use.

Much has been written during the past decade about the biopharmaceutical properties of, in particular, the solid dosage forms. In assessing the bioavailability of drugs in tablets and capsules, many researchers first have studied the absorption of drugs administered in solution. Since drugs are absorbed in their dissolved state, frequently it is found that the absorption rate of oral dosage forms decreases in the following order: aqueous solution > aqueous suspension > tablet or capsule. The bioavailability of a medicament, for oral ingestion and absorption, should be such that eventually all of the drug is absorbed as it passes through the gastrointestinal tract, regardless of the dosage form. Some formulation factors which may influence the bioavailability and pharmacokinetics of drugs in solution include concentration of the drug, volume of liquid administered, pH, buffer capacity and viscosity. Emulsions and suspensions are more complex systems and consequently the extent of absorption and pharmacokinetic parameters may be affected by a number of additional formulation factors such as surfactants, type of viscosity agent, particle size and particle-size distribution, polymorphism and solubility of drug in the oil phase. Specific examples are provided in Chapter 19. There are a number of reasons for formulating drugs in forms in which the drug is not in the molecular state. These are improved stability; improved taste; low water solubility, palatability and ease of administration. It becomes apparent, then, that each dosage form will have advantages and disadvantages.

Liquid preparations may be dispensed in one of three ways. The pharmacist may dispense the product in its original container, buy the product in bulk and repackage it at the time a prescription is presented by the patient or compound the solution, suspension or emulsion in the dispensary. Compounding may involve nothing more than mixing marketed products in the manner indicated on the prescription or, in specific instances, may require the incorporation of active ingredients in a logical and pharmaceutically acceptable manner into the aqueous or nonaqueous solvents which will form the bulk of the product.

The pharmacist, in the first instance, depends on the pharmaceutical manufacturer to produce a product that is effective, elegant and stable when stored under reasonably adverse conditions. Most manufacturers attempt to guarantee efficacy by evaluating their products in a scientifically acceptable manner but, in some instances, such efficacy is relative. For example, cough mixtures marketed by two different manufacturers may contain the same active ingredients and it becomes difficult to assess the relative merits of the two products. In such instances the commercial advantage gained by one over the other may be based on product acceptability and preference which includes such factors as color, odor, taste, pourability, uniformity and packaging. Two additional important factors which must be considered in formulations are the stability of active and other ingredients, and the prevention of microbial contamination.

The stability of the active ingredient in the final product is of prime concern to the formulator. In general, drug substances are less stable in aqueous media than in the solid dosage form and it is important, therefore, to properly stabilize and preserve, in particular those solutions, suspensions and emulsions that contain water. Certain simple chemical reactions can occur in these products. These may involve an ingredient-ingredient interaction which implies a poor formulation, a container-product interaction which may alter product pH and thus, for pH-sensitive ingredients, be responsible for the subsequent formation of precipitates or a direct reaction with water, ie, hydrolysis. The stability of pharmaceutical products is discussed in Chapter 38.

The more complicated reactions usually involve oxygen. Vitamins, essential oils and almost all fats and oils can be oxidized. Formulators usually use the word *autoxidation*

when the ingredient(s) in the product react with oxygen but without drastic external interference. Such reactions first must be initiated by heat, light (including ultraviolet radiant energy), peroxides or other labile compounds or heavy metals such as copper or iron. This initiation step results in the formation of a free radical (R*) which then reacts with oxygen.

$$R^* + O_2 \rightarrow RO_2^* \text{ (peroxy radical)}$$

$$RO_2^* + RH \rightarrow ROOH + R^*$$

The free radical thus is regenerated and reacts with more oxygen. This propagation step is followed by the termination reactions.

$$RO_2^* + RO_2^* \rightarrow \text{inactive product}$$

$$RO_2^* + R^* \rightarrow \text{inactive product}$$

$$R^* + R^* \rightarrow \text{inactive product}$$

The effect of trace metals can be minimized by using citric acid or EDTA ie, sequestering agents. Antioxidants, however, may retard or delay oxidation by reacting with the free radicals formed in the product. Examples of antioxidants are the propyl, octyl and dodecyl esters of gallic acid, butylated hydroxyanisole (BHA) and the tocopherols or vitamin E. For a more detailed approach to the prevention of oxidative deterioration in pharmaceuticals, the information provided by Connors *et al*[1] should be consulted. A description of many antioxidants is given in Chapter 80.

The problem of drug stability has been well-defined by pharmaceutical scientists, but during the past few years a secondary and, in some respects, more serious problem has confronted the manufacturer of liquid preparations. Such pharmaceutically diverse products as baby lotions and milk of magnesia have been recalled from the market because of microbial contamination. In a survey of retail packages of liquid antacid preparations containing magnesium hydroxide, it was found that 30.5% of the finished bottles were contaminated with *Pseudomonas aeruginosa*. The aerobic plate count ranged from less than 100 to 9,300,000 organisms/g. Kurup and Wan[2] describe many preparations that are not preserved adequately and thus are not able to resist microbial contamination. Other examples could be cited but the range of microorganisms which can contaminate the liquid preparation includes the *Salmonella* sp, *E coli*, certain *Pseudomonas* sp, including *P aeruginosa*, and *Staphylococcus aureus*. Bruch[3] describes the types of microorganisms found in various products and attempts to evaluate the hazards associated with the use of nonsterile pharmaceuticals. Coates[4] in a series of papers describes various interactions which must be considered when preservatives are selected.

The USP recommends that certain classes of products be tested for microbial count and for specified indicator microbial contaminants, eg, natural plant, animal and some mineral products, for freedom from *Salmonella* sp; oral solutions and suspensions, for freedom from *E coli*; articles applied topically, for freedom from *P aeruginosa* and *S aureus* and articles for rectal, urethral or vaginal administration, for yeasts and molds.

Products may become contaminated for a number of reasons.

The raw materials used in the manufacture of solutions, suspensions and emulsions are excellent growth media for bacteria. Water, in particular, must be handled with care but substances such as gums, dispersing agents, surfactants, sugars and flavors can be the carriers of bacteria which ultimately contaminate the product.

Equipment. Bacteria grow well in the nooks and crevices of pharmaceutical equipment (and in the simple equipment used in the dispensary). Such equipment should be cleaned thoroughly prior to use.

Environment and personnel can contribute to product contamination. Hands and hair are the most important carriers of contaminants. General cleanliness thus is vital. Head coverings must be used by those involved in the manufacturing process and face masks should be used by those individuals suffering from colds, coughs, hay fever and other allergic manifestations.

Packaging should be selected so that it will not contaminate the product and also will protect it from the environment.

Finally, consumer use may result in the introduction of microorganisms as a source of contamination, and this is of particular concern if the organism is pathogenic. The consumer should be instructed in the proper technique in order to minimize contamination, and the manufacturer should ensure, through the use of suitable challenge tests, that the product is preserved appropriately and will reduce a severe microbial challenge.

Most factors cited above relate to good manufacturing practice. However, the formulator should add a preservative to the product and decrease the probability of product contamination. If the product contains water, which is an important requirement for microbial growth, it almost is mandatory to include a preservative in the formulation. Nearly all products described in this chapter contain water and, thus, with certain exceptions, eg, aqueous acids, will support microbial growth. Microbes will grow in an aqueous solution, and in the aqueous phase of multiphase systems such as emulsions and suspensions. It must be stressed that the addition of an appropriate preservative in no way replaces good manufacturing practice but merely provides further assurance that the product will retain its pharmaceutically acceptable characteristics until it is used by the patient and for sometime thereafter.

The major criteria that should be considered in selecting a preservative are as follows: it should be effective against a wide spectrum of microorganisms, stable for its shelf life, nontoxic, nonsensitizing, compatible with the ingredients in the dosage form inexpensive and essentially relatively free of taste and odor.

In addition to the above discussion, there are a number of specific factors which should be taken into account when a preservative is selected:

1. The site of use, eg, external, internal or ophthalmic.
2. The pH of the liquid, as it may affect both the ionization of the preservative and its stability.
3. The solvent, as this will affect the solubility of the preservative.
4. Partitioning into the oil phase of an emulsion, thereby reducing the concentration in the aqueous phase where preservative action takes place.
5. Adsorption onto the solid phase of a suspension, thereby reducing the concentration in the aqueous phase.
6. Processing and packaging variables such as heat, order of addition of the ingredients, stirring or container materials.
7. Type of dosage form, eg, solution, emulsion or suspension.

Preservatives[5,6] may be grouped into a number of classes depending upon their molecular structure and only a few will be discussed. The reader should consult Chapter 80 or selected texts in the bibliography for further description.

Alcohols—Ethanol is useful as a preservative when it is used as a solvent; however, it does need a relatively high concentration, somewhat greater than 10%, to be effective. Too high a concentration may result in incompatibilities in suspension and emulsion systems. Propylene glycol also is used as a solvent in oral solutions and topical preparations, and it can function as a preservative in the range of 15 to 30%. It is not volatile like ethanol and is used frequently not only in solutions but also in suspensions and emulsions. Other alcohols used in lower concentrations, about 1%, for preservative action, include chlorobutanol and phenylethyl alcohol.

Acids—Benzoic acid has a low solubility in water, about 0.34% at 25°. The concentration range used for inhibitory action varies from 0.1% to 0.5%. Only the nonionized form is effective and therefore its use is restricted to preparations with a pH below 4.5. Sorbic acid also has a low solubility in water, 0.3% at 30°. Suitable concentrations for preservative action are in the range of 0.05 to 2%. Its preservative action is due to the nonionized form; consequently, it is only effective in acid media. Because of the double bond in its structure, it is subject to oxidation.

Esters—Parabens are esters of *p*-hydroxybenzoic acid and include the methyl, ethyl, propyl and butyl derivatives. The solubility in water decreases as the molecular weight increases from 0.25% for the methyl ester to 0.02% for the butyl ester. These compounds are used widely in pharmaceutical products and are effective and stable over a pH range of 4 to 8. They are employed at concentrations up to about 0.2%. Frequently, two esters are used in combination in the same preparation. This achieves a higher total concentration, and the mixture tends to be active against a wider range of microorganisms. Their activity is reduced in the presence of nonionic surface active agents due to binding. In alkaline solutions, ionization takes place and this reduces their activity; in addition, hydrolytic decomposition of the ester group occurs with a loss of activity.

Quaternary Ammonium Compounds—Benzalkonium chloride is a mixture consisting principally of the homologs $C_{12}H_{25}$ and $C_{14}H_{29}$. This preservative is used at a relatively low concentration, 0.002 to 0.02%, depending on the nature of the pharmaceutical product. This class of compounds has an optimal activity over the pH range of 4 to 10 and is quite stable at room temperature. Because of the cationic nature of this type of preservative, it is incompatible with many anionic compounds such as surfactants and can bind to nonionic surfactants. It is used generally in preparations for external use or those solutions which come in contact with mucous membranes.

It now should be obvious that when the pharmacist dispenses or compounds the various liquid preparations responsibility is assumed along, with the manufacturer, for the maintenance of product stability. The USP includes a section on stability considerations in dispensing, which should be studied in detail. Certain points are self-evident. Stock should be rotated and replaced if expiration dates on the label so indicate. Products should be stored in the manner indicated in the compendium; eg, in a cool place or a tight, light-resistant container. Further, products should be checked for evidence of instability. With respect to solutions, elixirs and syrups, color change, precipitation and evidence of microbial or chemical gas formation are major signs of instability. Emulsions may cream but if they break (ie, there is a separation of an oil phase) the product is considered to be unstable. Sedimentation and caking are primary indications of instability in suspensions. The presence of large particles may mean that excessive crystal growth has occurred.

The USP states that if the product must be repackaged, care and the container specified by the compendium must be used. For example, a suitably opaque plastic container should be used if a light-resistant container is specified. If a product is diluted, or where two products are mixed, the pharmacist should use his or her knowledge to guard against incompatibility and instability. Oral antibiotic preparations constituted into liquid form should never be mixed with other products. If the chemical stability of extemporaneously prepared liquid preparations is unknown, their use should be minimized and every care taken to insure that product characteristics will not change during the time it must be used by the patient.

Because of the number of excipients and additives in these preparations, it is recommended that all the ingredients be listed on the container to reduce the risks which confront hypersensitive patients when these products are administered. Finally, the pharmacist should inform the patient regarding the appropriate use of the product, the proper storage conditions and the time after which it should be discarded.

Solutions

Aqueous Solutions

A solution is a homogeneous mixture that is prepared by dissolving a solid, liquid or gas in another liquid and represents a group of preparations in which the molecules of the solute or dissolved substance are dispersed among those of the solvent. Solutions also may be classified on the basis of physical or chemical properties, method of preparation, use, physical state, number of ingredients and particle size. The narrower definition in this subsection limits the solvent to water and excludes those preparations that are sweet and/or viscid in character and nonaqueous solutions. This section includes, therefore, those pharmaceutical forms that are designated as *Water*, *Aromatic Waters*, *Aqueous Acids*, *Solutions*, *Douches*, *Enemas*, *Gargles*, *Mouthwashes*, *Juices*, *Nasal Solutions*, *Otic Solutions* and *Irrigation Solutions*.

Water

The major ingredient in most of the dosage forms described herein is water. It is used both as a vehicle and as a solvent for the desired flavoring or medicinal ingredients. Its tastelessness, freedom from irritating qualities and lack of pharmacological activity make it ideal for such purposes. There is, however, a tendency to assume that its purity is constant and that it can be stored, handled and used with a minimum of care. While it is true that municipal supplies must comply with Environmental Protection Agency (EPA) regulations (or comparable regulations in other countries), drinking water *must* be repurified before it can be used in pharmaceuticals. For further information on water, see Chapter 23.

Five of the six solvent waters described in the USP are used in the preparation of parenterals, irrigations or inhalations. *Purified Water* must be used for all other pharmaceutical operations, dosage forms and, as needed, in all USP tests and assays. It must meet rigid specifications for chemical purity. Such water may be prepared by distillation, by use of ion-exchange resins or by reverse osmosis.

A wide variety of commercially available stills are used to produce distilled water. The end use of the product dictates the size of the still and extent of pretreatment of the drinking water introduced into the system. A description of stills is provided in Chapter 87. Such water may be sterile provided the condenser is sterile, but to be called sterile it must be subjected to a satisfactory sterilization process. However, it has been shown that *P. aeruginosa* (and other microorganisms) can grow in the distilled water produced in hospitals. The implications of this are obvious. Sterile water may be sterile at the time of production but may lose this characteristic if it is stored improperly. Hickman *et al*,[7] by regrouping the components of conventional distillation equipment, have described a method for the continuous supply of sterile, ultrapure water. Quality-control procedures for monitoring the microbiological quality of water should be performed in the pharmaceutical manufacturer's production facilities.

The major impurities in water are calcium, iron, magnesium, manganese, silica and sodium. The cations usually are combined with the bicarbonate, sulfate or chloride anions. "Hard" waters are those that contain calcium and magnesium cations. Bicarbonates are the major impurity in "alkaline" waters.

Ion-exchange (deionization, demineralization) processes will remove most of the major impurities in water efficiently and economically. A cation exchanger, H_2R, first converts bicarbonates, sulfates and chlorides to their respective acids, eg,

$$\left.\begin{matrix} CaSO_4 \\ MgSO_4 \\ Na_2SO_4 \end{matrix}\right| + H_2R \rightarrow \left|\begin{matrix} Ca \\ Mg \\ Na_2 \end{matrix}\right| R + H_2SO_4$$

$$\left.\begin{matrix} Ca(HCO_3)_2 \\ Mg(HCO_3)_2 \\ 2NaHCO_3 \end{matrix}\right| + H_2R \rightarrow \left|\begin{matrix} Ca \\ Mg \\ Na_2 \end{matrix}\right| R + 2H_2CO_3$$

Carbonic acid decomposes to carbon dioxide (which is removed by aeration in the decarbonator) and water.

The anion exchanger may contain either a weakly basic or a strongly basic anion resin. These adsorb sulfuric, hydrochloric and nitric acids. Chemical reactions may involve complete adsorption or an exchange with some other anion.

$$H_2SO_4 + A \rightarrow A \cdot H_2SO_4$$

If the resin contains a hydroxyl group, water is formed during the purification process.

$$H_2SO_4 + 2AOH \rightarrow A_2SO_4 + 2H_2O$$

CHAPTER 87

Parenteral Preparations

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The distinctive characteristics of parenteral (Gk, *para enteron*, beside the intestine) dosage forms of drugs will be discussed in this chapter. These dosage forms differ from all other drug dosage forms because of the unique requirements imposed because they are injected directly into body tissue through the primary protective system of the human body, the skin and mucous membranes. Therefore, they must be exceptionally pure and free from physical, chemical and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice good manufacturing practices (GMPs) in the manufacture of parenteral dosage forms and upon pharmacists to practice good aseptic practices (GAPs) in dispensing them for administration to patients.

Many of the newer drugs, particularly these derived from the new developments in biotechnology, can only be given parenterally because they are inactivated in the gastrointestinal tract, when given by mouth. Further, the potency and specificity of many of these drugs requires strict control of their administration to the patient. A parenteral route of administration meets both of these critical requirements.

This chapter will begin with a brief review of the historical events contributing to the development of this distinctive dosage form. Consideration will then be given to some of the distinguishing characteristics of these dosage forms and how they are administered to patients. The majority of the remainder of the chapter will discuss the various factors required for the preparation of a pure, safe and effective parenteral product.

History[1]

One of the most significant events in the beginnings of parenteral therapy was the first recorded injection of drugs into the veins of living animals, in about 1657, by the architect Sir Christopher Wren. From such a very crude beginning, the technique for intravenous injection and knowledge of the implications therefore developed slowly during the next century and a half. In 1855 Dr Alexander Wood of Edinburgh described what was probably the first subcutaneous injection of drugs for therapeutic purposes using a true hypodermic syringe.

The latter half of the 19th century brought increasing concern for safety in the administration of parenteral solutions, largely because of the work of Robert Koch and Luis Pasteur. While Charles Chamberland was developing both hot-air and steam sterilization techniques and the first bacteria-retaining filter (made of unglazed porcelain), Stanislaus Limousin was developing a suitable container, the all-glass ampul. In the middle 1920s Dr Florence Seibert provided proof that the disturbing chills and fever which often followed the intravenous injection of drugs was caused by potent products of microbial growth, pyrogens, which could be eliminated from water by distillation and from glassware by heating at elevated temperatures.

Of the technical developments that have contributed to the high quality standards currently achievable in the preparation of parenteral dosage forms, the two that have probably contributed most are the development of HEPA-filtered laminar airflow and the development of membrane microfiltration for solutions. The former made it possible to achieve ultraclean environmental conditions for processing from solutions by filtration both viable and nonviable particles of microbial size and smaller. However, many other developments in recent years have produced an impressive advance in the technology associated with the safe and reliable preparation of parenteral dosage forms. The following list identifies a few of the events which have contributed to that development.

1926—Parenterals were accepted for inclusion in the fifth edition of the *National Formulary*.

1933—The practical application of freeze-drying to clinical materials was accomplished by a team of scientists at the University of Pennsylvania.

1938—The Food, Drug and Cosmetic Act was passed by Congress, establishing the Food and Drug Administration (FDA).

1944—The sterilant ethylene oxide was discovered.

1946—The Parenteral Drug Association was organized.

1961—The concept of laminar airflow was developed by WJ Whitfield.

1962—The FDA was authorized by Congress to establish current good manufacturing practice (CGMP or GMP) regulations.

1965—Total parenteral nutrition (TPN) was developed by SJ Dudrick.

1972—The Limulus Amebocyte Lysate test for pyrogens in parenteral products was developed by JF Cooper.

1974—The concept of validation of processes used in the manufacture of parenteral products was introduced by the FDA.

1977—The principles for clean-in-place (CIP) and steam-in-place (SIP) were introduced.

Early 1980s—Home Health Care emerged as an alternative for patients whose health status permitted release from a hospital to care in the home environment.

1982—Insulin, derived through the new discipline of biotechnology, ushered in the drug class of polypeptides with their inherent stability challenges for parenteral dosage-form development.

1987—Parametric release was accepted by the FDA for selected products terminally sterilized by a validated heat process.

The FDA published *Guideline on Sterile Products Produced by Aseptic Processing*, one of several nonregulatory publications to help industry know what the FDA considers to be acceptable.

Late 1980s—The development of computer capabilities has led to the automation of many process operations and to a revolution in documentation and recordkeeping.

1991—The FDA proposed requiring manufacturers to use a terminal sterilization process when preparing a sterile drug product unless such a process adversely affects the drug product.

Administration

Injections may be classified in six general categories:

1. Solutions ready for injection.
2. Dry, soluble products ready to be combined with a solvent just prior to use.
3. Suspensions ready for injection.
4. Dry, insoluble products ready to be combined with a vehicle just prior to use.
5. Emulsions.
6. Liquid concentrates ready for dilution prior to administration.

These injections may be administered by such routes as intravenous, subcutaneous, intradermal, intramuscular, intra-

articular and intrathecal. The nature of the product will determine the particular route of administration that may be employed. Conversely, the desired route of administration will place requirements on the formulation. For example, suspensions would not be administered directly into the blood stream because of the danger of insoluble particles blocking capillaries. Solutions to be administered subcutaneously require strict attention to tonicity adjustment, otherwise irritation of the plentiful supply of nerve endings in this anatomical area would give rise to pronounced pain. Injections intended for intraocular, intraspinal, intracisternal and intrathecal administration require the highest purity standards because of the sensitivity of tissues encountered to irritant and toxic substances.

When compared with other dosage forms, injections possess select advantages. If immediate physiological action is needed from a drug, it usually can be provided by the intravenous injection of an aqueous solution. Modification of the formulation or another route of injection can be used to slow the onset and prolong the action of the drug. The therapeutic response of a drug is controlled more readily by parenteral administration since the irregularities of intestinal absorption are circumvented. Also, since the drug normally is administered by a professionally trained person, it confidently may be expected that the dose was actually and accurately administered. Drugs can be administered parenterally when they cannot be given orally because of the unconscious or uncooperative state of the patient, or because of inactivation or lack of absorption in the intestinal tract. Among the disadvantages of this dosage form are the requirement of asepsis at administration, the risk of tissue toxicity from local irritation, the real or psychological pain factor and the difficulty in correcting an error, should one be made. In the latter situation, unless a direct pharmacological antagonist is immediately available, correction of an error may be impossible. One other disadvantage is that daily or frequent administration poses difficulties, either for the patient to visit a professionally trained person or to learn to inject oneself. However, the advent of home health care as an alternative to extended institutional care has mandated the development of programs for training lay persons to administer these dosage forms.

Parenteral Combinations

During the administration of large-volume parenterals (LVPs), such as 1000-mL of 0.9% sodium chloride solution, it is common practice for a physician to order the addition of a small-volume therapeutic parenteral (SVP), such as an antibiotic, to avoid the discomfort for the patient of a separate injection. While the pharmacist is the most qualified health professional to be responsible to prepare such combinations, as is clearly stated in the Hospital Accreditation Manual of the Joint Commission on Accreditation of Healthcare Organizations,[2] interactions among the combined products can be troublesome even for the pharmacist. In fact, incompatibilities can occur and cause inactivation of one or more ingredients or other undesired reactions. In some instances incompatibilities are visible as precipitation or color change, but in other instances there may be no visible effect.

The many potential combinations present a complex situation even for the pharmacist. To aid in making decisions concerning potential problems, a valuable compilation of relevant data has been assembled by Trissel,[3] and is regularly updated. Further, the advent of computerized data storage and retrieval systems has provided a means to organize and gain rapid access to such information. Further information on this subject may be found in Chapter 88.

As studies have been undertaken and more information has been gained, it has been shown that knowledge of variable factors such as pH and the ionic character of the active constituents aids substantially in understanding and predicting potential incompatibilities. Kinetic studies of reaction rates may be used to describe or predict the extent of degradation. Ultimately, a thorough study should be undertaken of each therapeutic agent in combination with other drugs and IV fluids, not only of generic but of commercial preparations, from the physical, chemical and therapeutic aspects.

Ideally, no parenteral combination should be administered unless it has been studied thoroughly to determine its effect on the therapeutic value and the safety of the combination. However, such an ideal situation may not exist. Nevertheless, it is the responsibility of the pharmacist to be as familiar as possible with the physical, chemical and therapeutic aspects of parenteral combinations and to exercise the best possible judgment as to whether or not the specific combination extemporaneously prescribed is suitable for use in a patient.

General Considerations

An inherent requirement for parenteral preparations is that they be of the very best quality and provide the maximum safety for the patient. Therefore, whether they are prepared from commercially available sterile components, as is usually the case in hospital pharmacies and similar sites, or from nonsterile ingredients in a manufacturing mode, as is the case in the pharmaceutical industry, the persons responsible for their preparation must apply their skills intelligently and diligently. Further, the possession and application of high moral and professional ethics on the part of the persons responsible is the ingredient most vital to achieving the desired quality in the products prepared.

The preparation of parenteral products from sterile components in pharmacies of hospitals and similar sites is discussed further in Chapter 88. In this chapter emphasis will be placed on the preparation of parenteral products from non-sterile components in the highly technologically advanced plants of the pharmaceutical industry, using GMP principles. In the pursuit of GMP, consideration should be given to:

1. Ensure the personnel responsible for assigned duties are capable and qualified to perform them.
2. Ensure that ingredients used in compounding the product have the required identity, quality and purity.
3. Validate critical processes to be sure that the equipment used and the processes followed will ensure that the finished product will have the qualities expected.
4. Maintain a production environment suitable for performing the critical processes required, addressing such matters as orderliness, cleanliness and asepsis.
5. Confirm through adequate quality-control procedures that the finished products have the required potency, purity and quality.
6. Establish through appropriate stability evaluation that the drug products will retain their intended potency, purity and quality until the established expiration date.
7. Ensure that processes are always carried out in accord with established, written procedures.
8. Provide adequate conditions and procedures for the prevention of mixups.
9. Establish adequate procedures, with supporting documentation, for investigating and correcting failures or problems in production or quality control.
10. Provide adequate separation of quality-control responsibilities from those of production to assure independent decision making.

The pursuit of GMP is an ongoing effort which must flex with new technological developments and new understanding of existing principles. Because of the extreme importance of quality in health care of the public, the US Congress has given the responsiblity of regulatory scrutiny over the manufacture and distribution of drug products to the FDA. Therefore, the operations of the pharmaceutical industry are subject to the oversite of the FDA and, with respect to manufacturing practices, to the application of the CGMPs.[4] These regulations are discussed more fully in Chapter 110.

In concert with the pursuit of GMPs, the pharmaceutical industry has shown initiative and innovation in the extensive technological development and improvement in quality, safety and effectiveness of parenteral dosage forms in recent years. Further, outstanding innovative development in drug-delivery

systems is occurring. These factors have been additive in providing the public with outstanding parenteral dosage forms of drugs at this time in history.

General Manufacturing Process

The preparation of a parenteral product may be considered to encompass four general areas as follows:

1. Procurement and selection o the components and containers.
2. Production facilities and procedures.
3. Control of quality.
4. Packaging and labeling.

These components of the product to be procured include vehicles, solutes, containers and closures. The steps constituting production include maintaining facilities and equipment, preparing and controlling the environment, cleaning the containers and equipment, preparing the product, filtering the solution, filling containers with the product, sealing the containers and sterilizing the product. The control of quality includes the evaluation of the components, qualification of equipment, validation of processes, determination that the production has been executed within prescribed requirements and performance of necessary evaluative tests on the finished product. The final area of packaging and labeling includes all steps necessary to identify the finished product and enclose it in such manner that it is safely and properly prepared for sale and delivery to the user. The remainder of this chapter will be organized in accord with these four general areas, with emphasis on the first two areas.

Components and Containers

Establishing specifications to ensure the quality of each of the components of an injection is essential. These specifications will be coordinated with the requirements of the specific formulation and will not necessarily be identical for a particular component if used in several different formulations. For example, particle-size control may be necessary for powders used in formulating a suspension but be relatively unimportant for preparing a solution.

The most stringent chemical-purity requirements normally will be encountered with aqueous solutions, particularly if the product is to be sterilized at an elevated temperature where reaction rates will be accelerated greatly. Modification of aqueous vehicles to include a glycol, for example, usually will reduce reaction rates. Dry preparations pose relatively few reaction problems but may require definitive physical specifications for ingredients that must have certain solution or dispersion characteristics when a vehicle is added.

Containers and closures are in prolonged, intimate contact with the product and may release substances into or remove ingredients from the product. Assessment and selection of containers and closures is a necessary part of product formulation to ensure that the product retains its purity, potency and quality during the intimate contact with the container throughout its shelf-life. Administration devices that come in contact with the product should be assessed and selected with the same care as are containers and closures, even though the contact period is usually brief.

Vehicles

Since most liquid injections are quite dilute, the component present in the highest proportion is the vehicle. A vehicle normally has no therapeutic activity and is nontoxic. However, it is of great importance in the formulation since it presents to body tissues the form of the active constituent for absorption. Absorption normally occurs most rapidly and completely when a drug is presented as an aqueous solution. Modification of the vehicle with water-miscible liquids or substitution with water-immiscible liquids normally decreases the rate of absorption. Absorption from a suspension may be affected by such factors as the viscosity of the vehicle, its capacity for wetting the solid particles, the solubility equilibrium produced by the vehicle and the distribution coefficient between the vehicle and aqueous body systems.

The vehicle of greatest importance for parenteral products is water. Water of suitable quality for compounding and rinsing product contact surfaces may be prepared either by distillation or by reverse osmosis, to meet USP specifications for Water for Injection (WFI). Only by these two methods is it possible to separate adequately various liquid, gas and solid contaminating substances from water. These two methods for preparation of WFI will be discussed in this Chapter. It should be noted that there is no unit operation more important and none more costly to install and operate than the one for the preparation of WFI.

Preparation of Water for Injection (WFI)

The source water can be expected to be contaminated with natural suspended mineral and organic substances, dissolved mineral salts, colloidal silicates and industrial chemicals. The degree of contamination will vary with the source and will be markedly different whether obtained from a well or from surface sources, such as a stream or lake. Therefore, this water normally is not of sufficient purity to prepare WFI directly. Hence, the source water usually must be pretreated by one or a combination of the following treatments: chemical softening, filtration, deionization, carbon adsorption or reverse osmosis purification. Space does not permit discussion of these processes here, but the interested reader is referred elsewhere for this information.[5,6]

In general, a conventional still consists of a boiler (evaporator) containing feed water (distilland); a source of heat to vaporize the water in the evaporator; a headspace above the level of distilland with condensing surfaces for refluxing the vapor, thereby returning nonvolatile impurities to the distilland, a means for eliminating volatile impurities before the hot water vapor is condensed; and a condenser for removing the heat of vaporization, thereby converting the water vapor to a liquid distillate.

The specific construction features of a still and the process specifications markedly will affect the quality of distillate obtained from a still. Those required for producing high-purity water, such as WFI, must be considerably more stringent than those required for Purified Water USP. Among the factors that must be considered are:

1. The quality of the feed water will affect the quality of the distillate. Controlling the quality of the feed water is essential for meeting the required specifications for the distillate.
2. The size of the evaporator will affect the efficiency. It should be large enough to provide a low vapor velocity, thus reducing the entrainment of the distilland either as a film on vapor bubbles or as separate droplets.
3. The baffles (condensing surfaces) determine the effectiveness of refluxing. They should be designed to remove efficiently the entrainment at optimal vapor velocity, collecting and returning the heavier droplets contaminated with the distilland.
4. Redissolving volatile impurities in the distillate reduces its purity. Therefore, they should be separated efficiently from the hot water vapor and eliminated by aspirating them to the drain or venting them to the atmosphere.
5. Contamination of the vapor and distillate from the metal parts of the still can occur. Present standards for high-purity stills are that all parts contacted by the vapor or distillate should be constructed of metal coated with pure tin, 304 or 316 stainless steel or chemically resistant glass.